Genetics in the brain

Using animals in neuroscience

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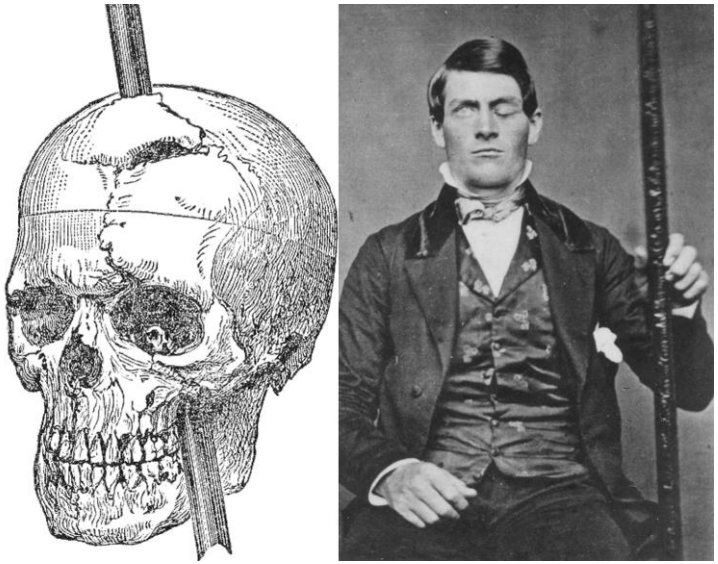
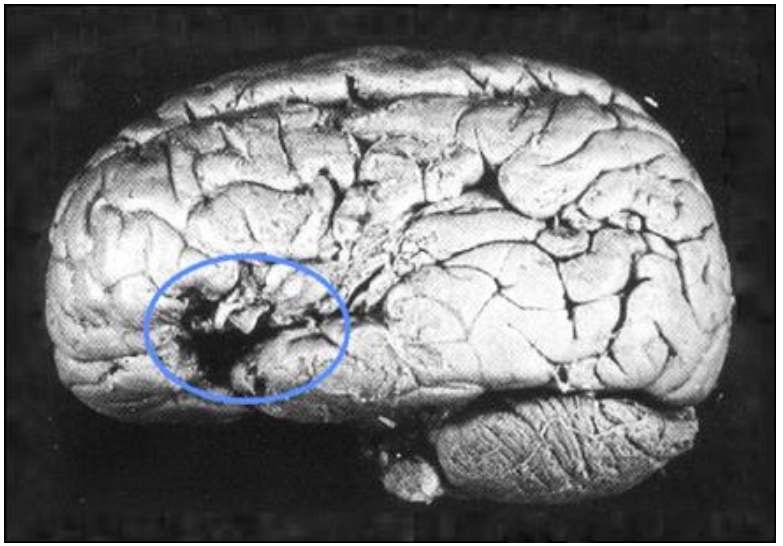
Dept. Clinical Genetics
Erasmus MC
University Medical Center Rotterdam

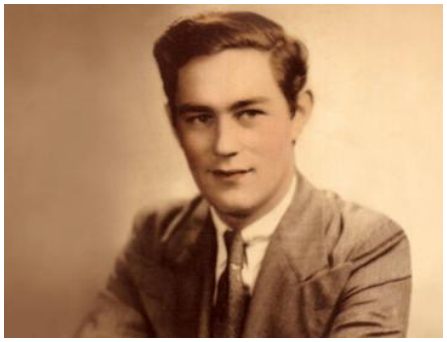
Famous patients in Neuroscience



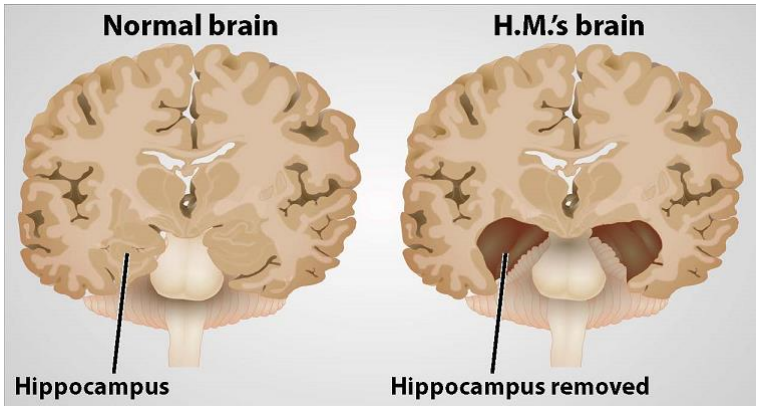
Phineas Gage



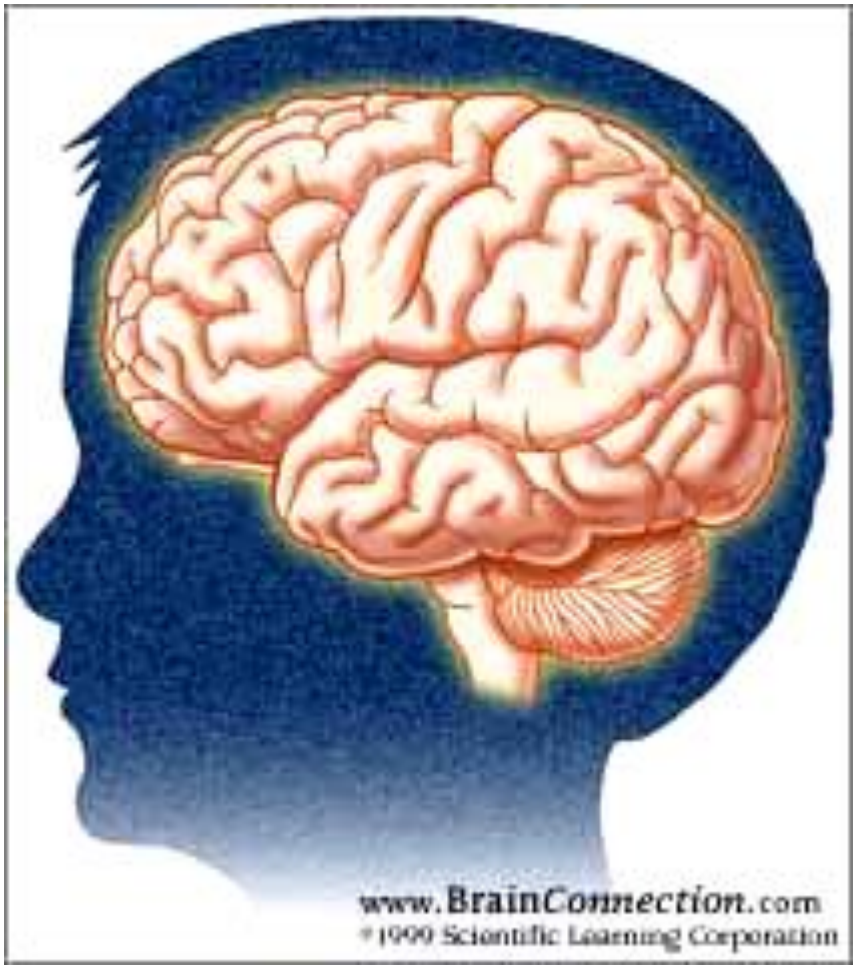
Monsieur Tan

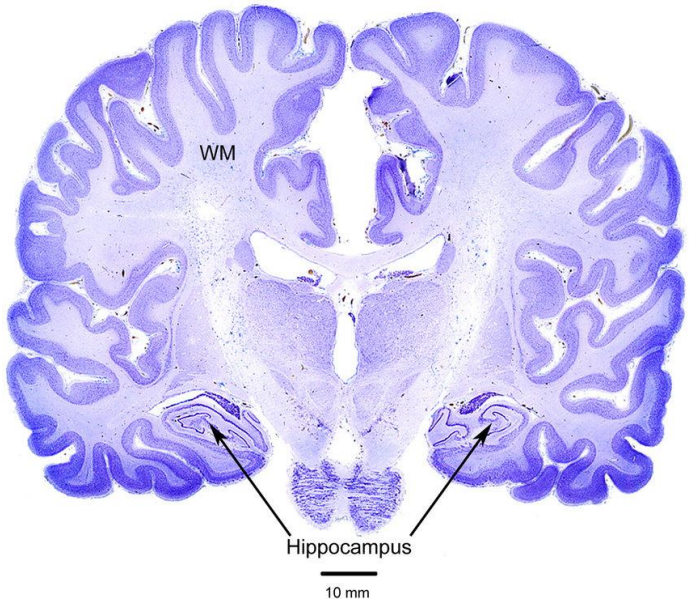


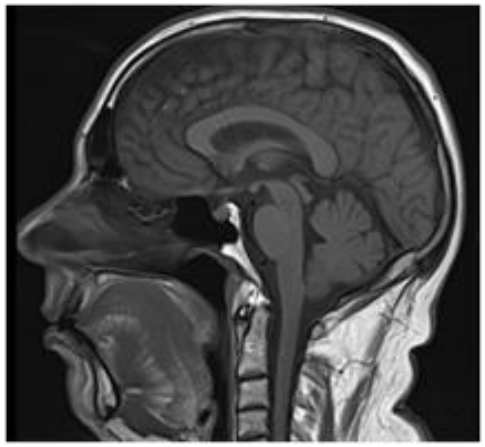
H.M.

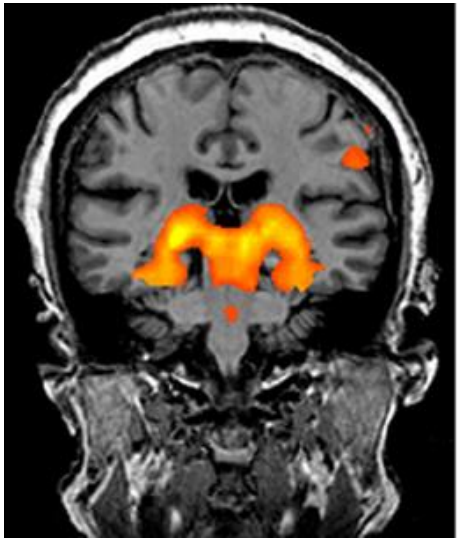


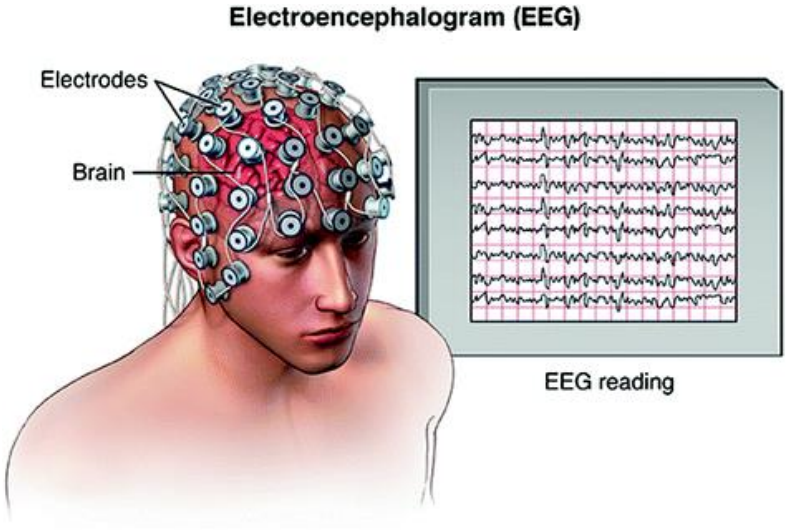
The ideal study subject:




WM
Hippocampus
10 mm

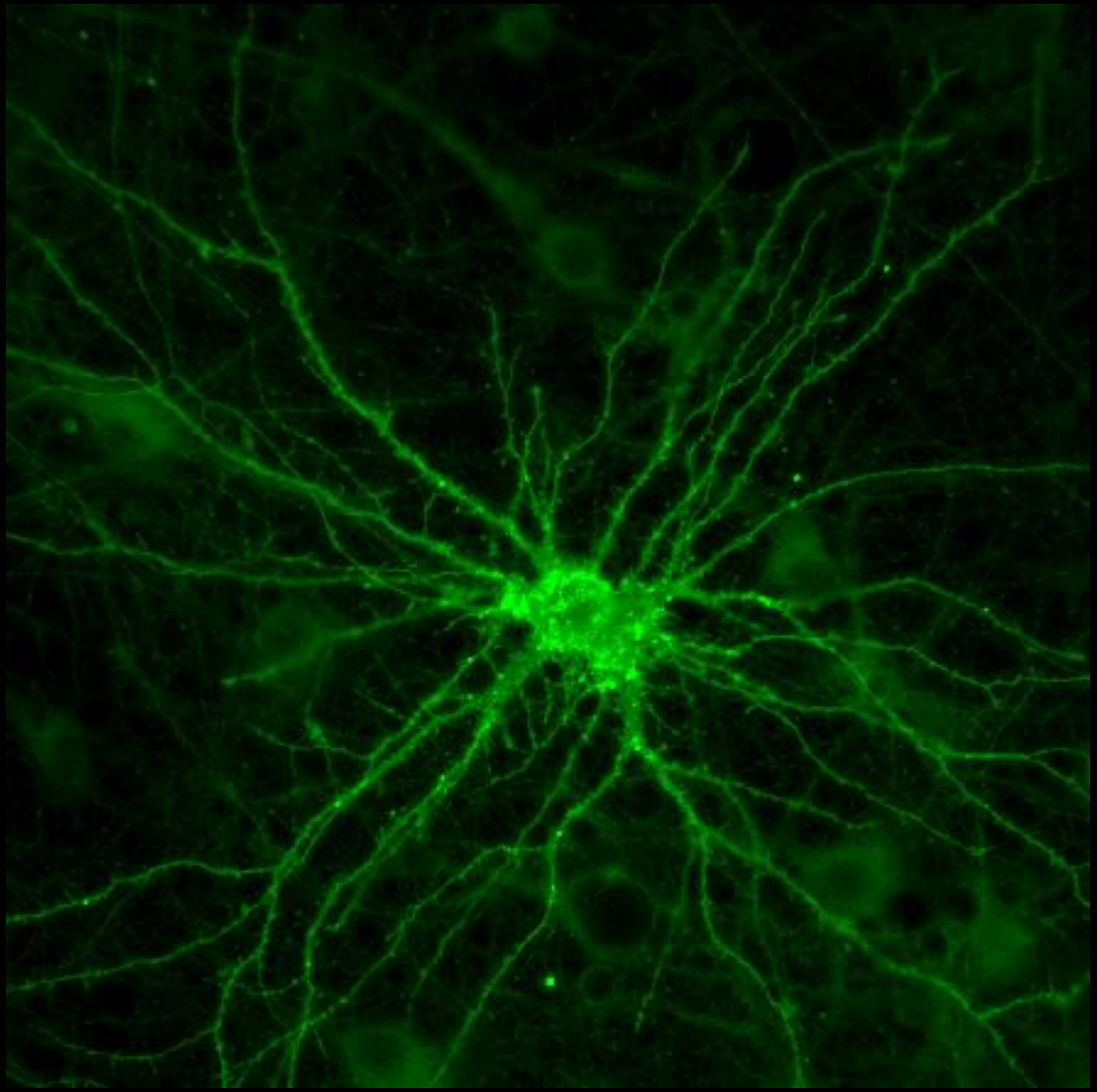





Electroencephalogram (EEG)
Electrodes
Brain
EEG reading

But we want more…

How does the brain work and what happens in neurological disorders?



How to study the molecular and cellular mechanisms of the brain?

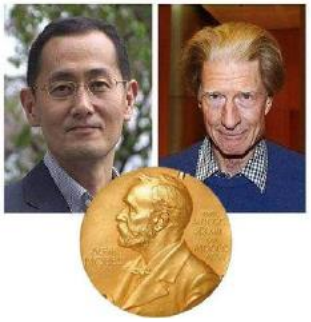
The Nobel Prize in Physiology or Medicine 2012

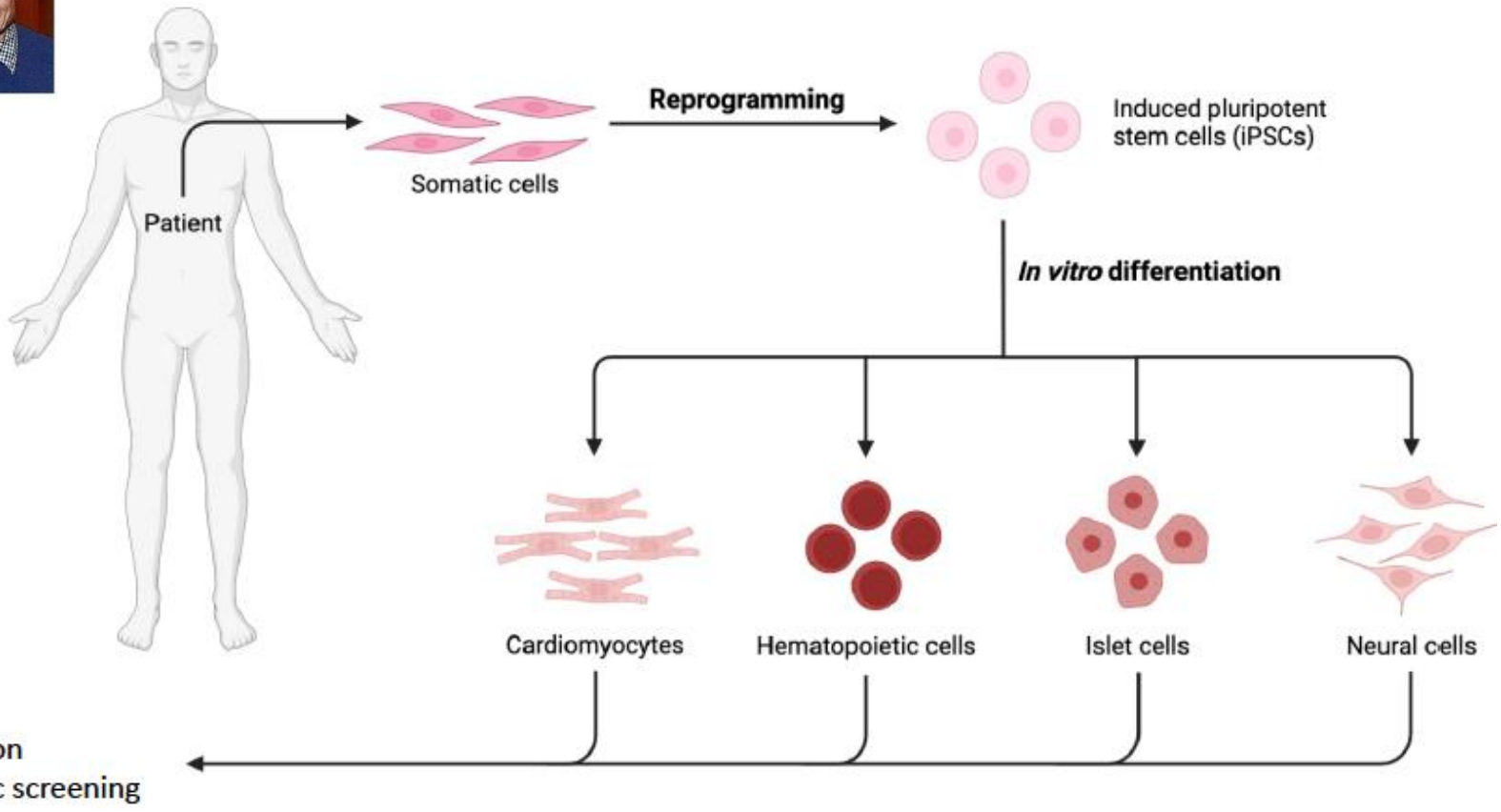
jointly to

John B. Gurdon and Shinya Yamanaka

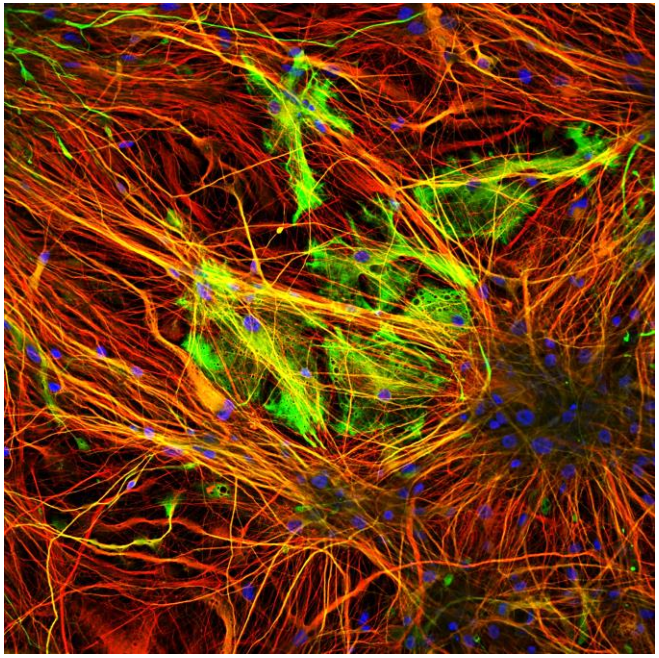
for the discovery that mature cells can be reprogrammed to become pluripotent

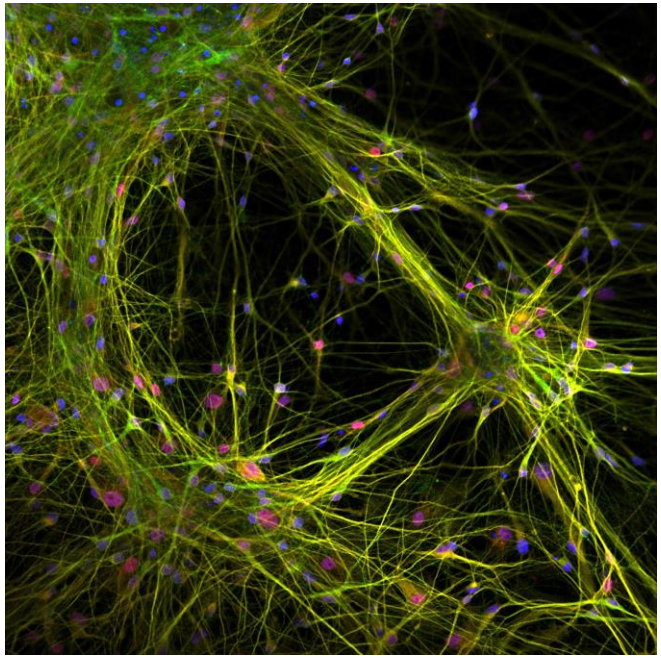
Brains in a dish

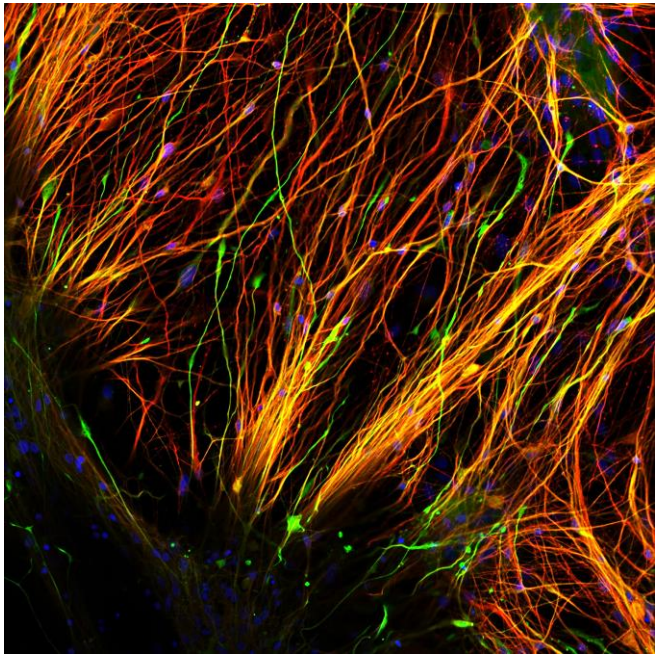


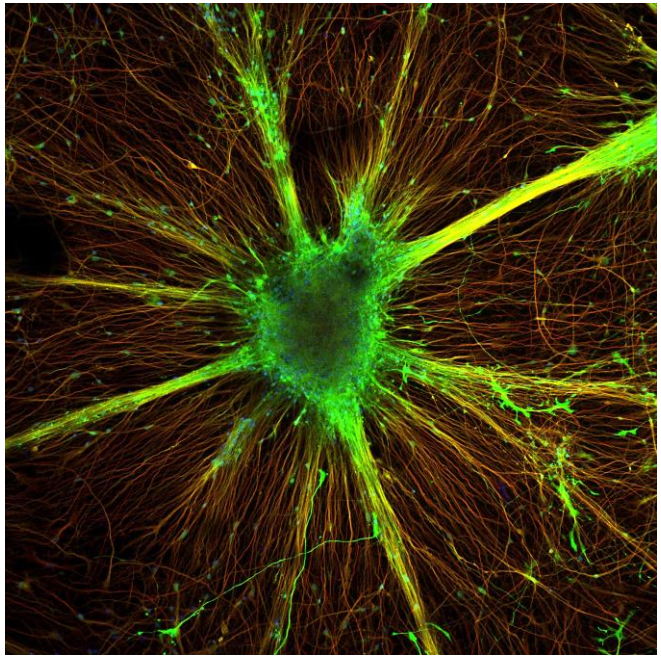


Erasmus MC

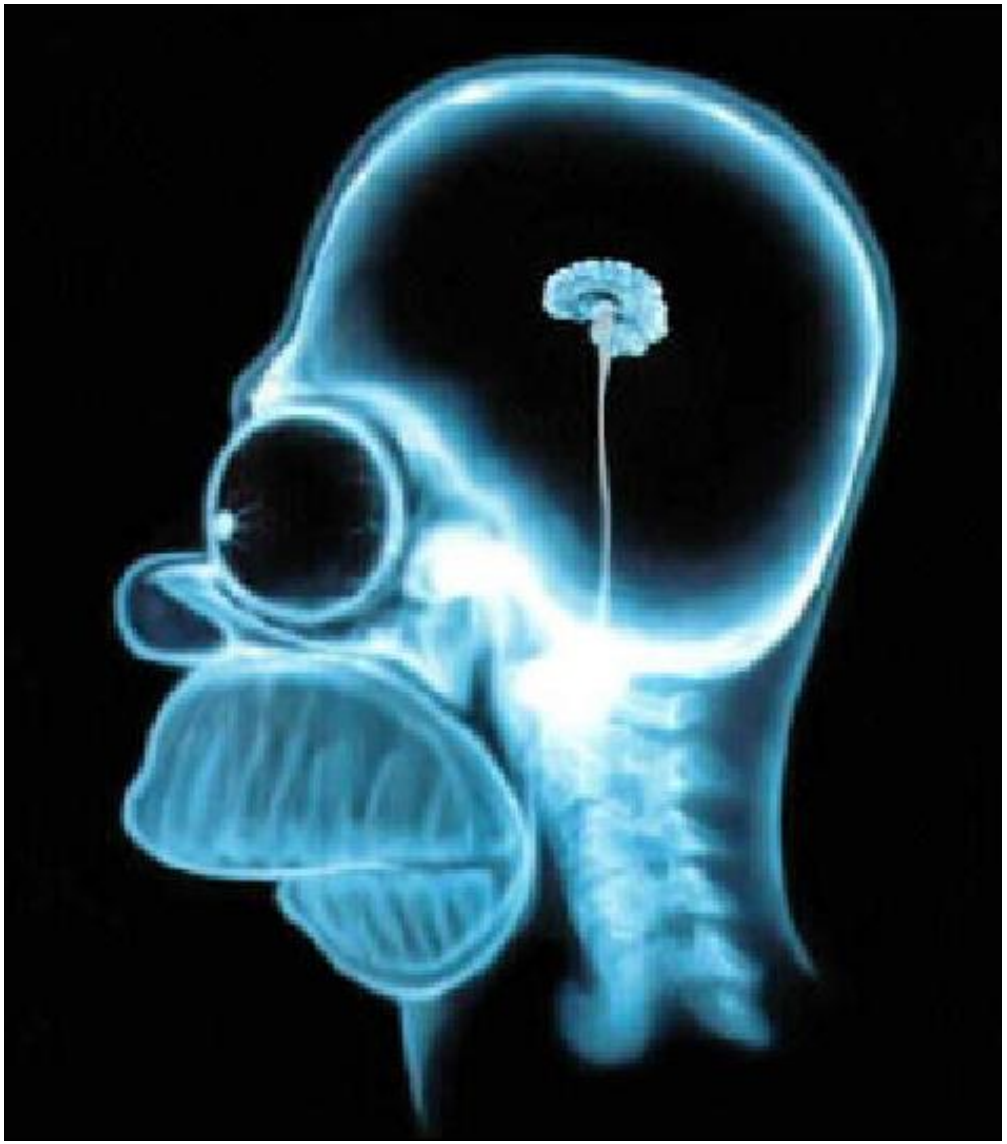








We need a model.

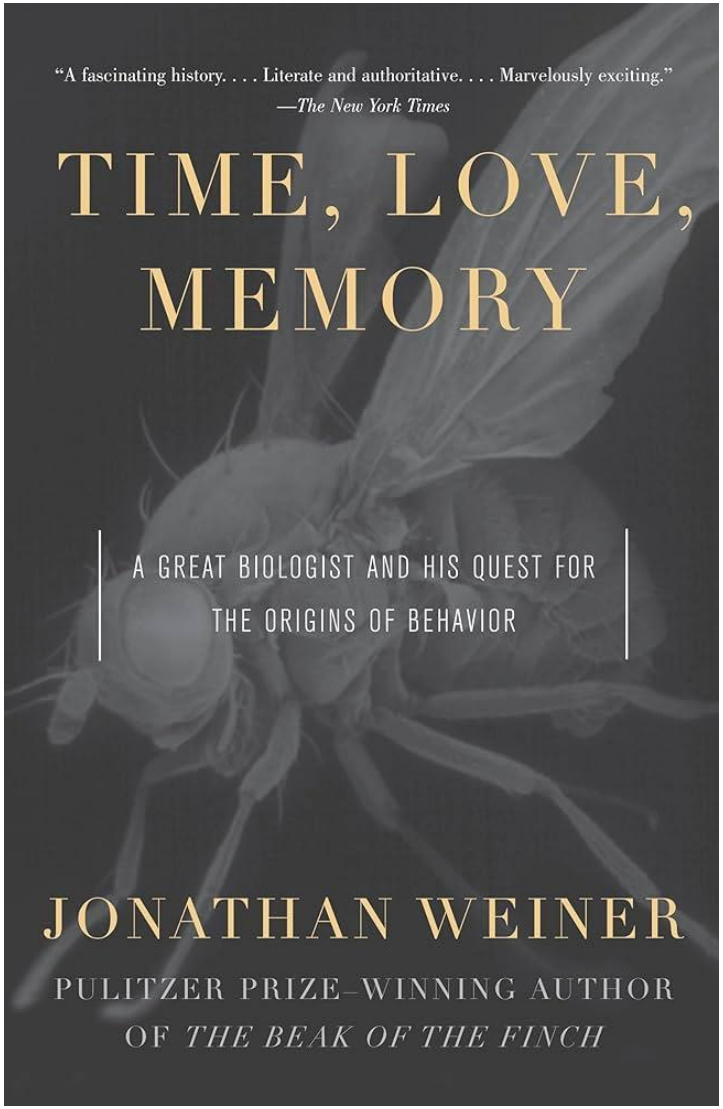


MRI scan of Homer

Available models

- *Many ethical obstacles*
- *Impractical (and very expensive)*
- *Not possible to study congenital defects*

Fruit fly aka Drosophila Melanogaster



Science: Moonwalker fly

Erasmus MC

Neuronal Control of *Drosophila* Walking Direction

Salil S. Bidaye,* Christian Machacek, Yang Wu,† Barry J. Dickson†‡

www.sciencemag.org SCIENCE VOL 344 4 APRIL 2014

Worm en Alzheimer (The guardian, Feb, 2016)

GM worm study provides 'powerful first step' towards preventing Alzheimer's

Research is at a very early stage, but scientists are hopeful that a 'neurostatin' preventative drug for neurological conditions will become a reality

Researchers modified nematode worms to develop Alzheimer's-like symptoms, and then applied anti-cancer drug, bexarotene, at various stages of the disease. Photograph: PA

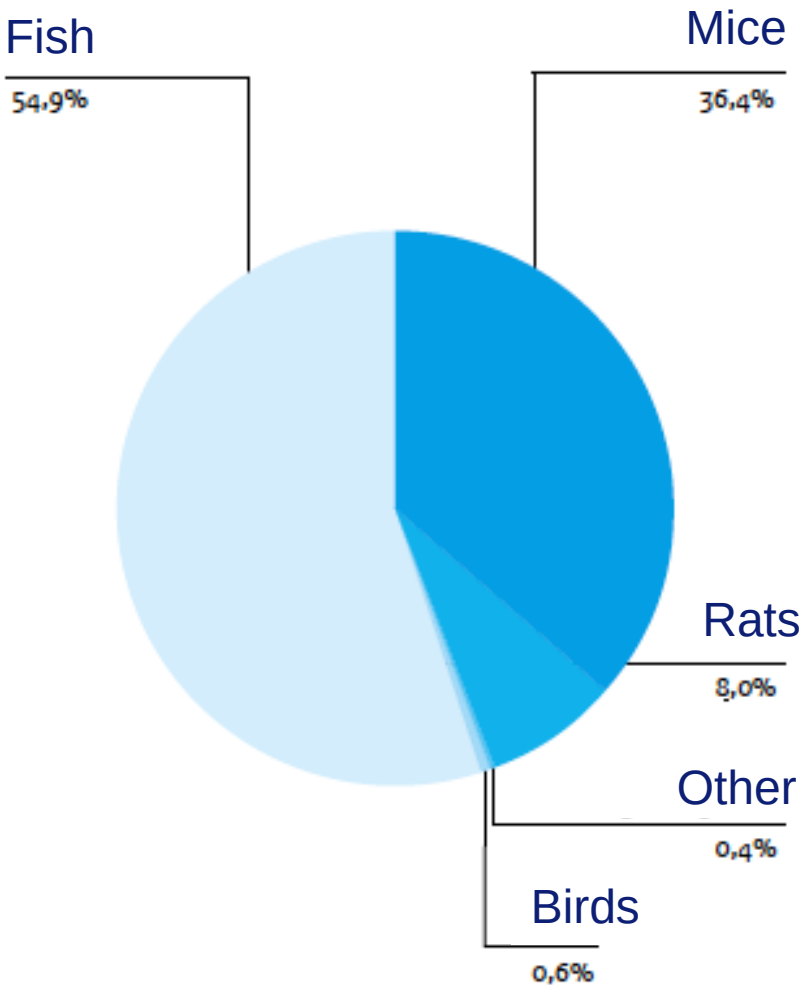
Zebrafish use to understand Alzheimer's disease

Zebravisjes helpen ziekte van Alzheimer ontrafelen

19 augustus 2014

Nieuwe fundamentele kennis over de regulatie van stamcellen in het zenuwweefsel van embryonale zebravisjes leidt tot verrassende inzichten in neurodegeneratieve ziekteprocessen in het menselijke brein. Een nieuwe studie van onderzoekers van het Vlaams Instituut voor Biotechnologie en KU Leuven identificeert de molecules die aan de basis van dit proces liggen.

Current animal use in research in the Netherlands



Goal of the experiment

- Fundamental scientific research (37,8%)
- Toxicity research required by law (29,4%)
- Preclinical research (28%)
- Teaching (3,7%)

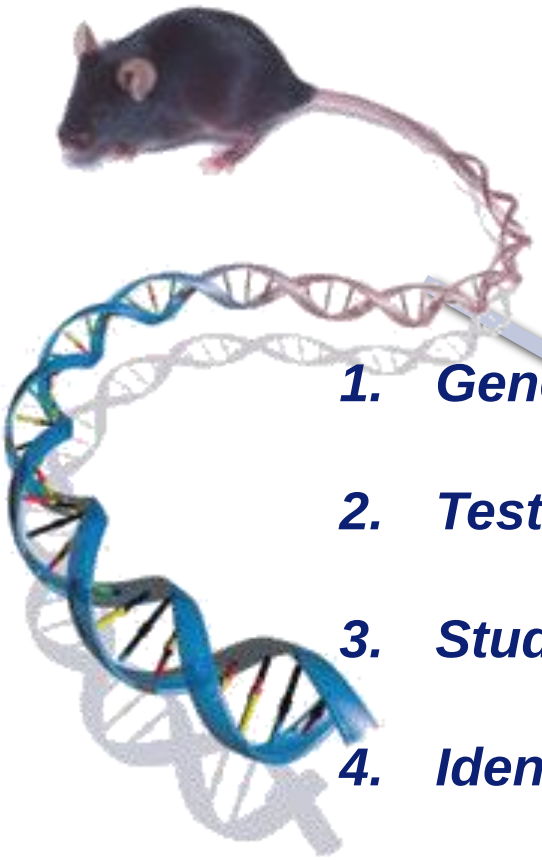
What do we do?

- Neuroscience research studying disorders of the brain
- Model: Mus Musculus (mouse)

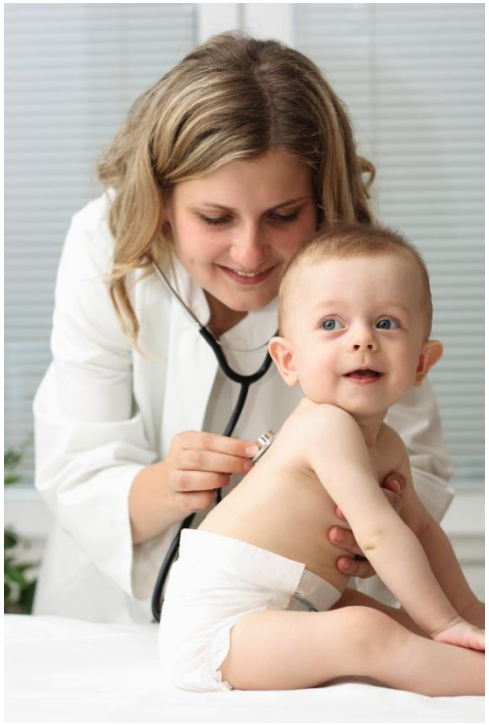
Why mice?

- ✓ *Mouse versus human brain show high similarity (macro- and microscopic as well as molecular)*
- ✓ *Genetically modifiable*
- ✓ *Inbred strains*
- ✓ *Behavior, electrophysiological and molecular studies*

From mouse to men



1. *Generate a mouse model for the disease*
2. *Test the validity of the model*
3. *Study the mechanism*
4. *Identify a potential treatment*
5. *Test in patients*



Can I use any mouse at any timepoint?

Erasmus MC

European Animal Research Association

Animal research in the European Union (EU) is regulated under Directive 2010/63/EU on the protection of animals used for scientific purposes.

The final aim of the Directive is to replace all animal research with non-animal methods of research, such as organoids or through computer simulations.

When can we use animals?

✓*If there is no alternative available.*

✓*If the scientific and societal benefit overrules the discomfort of the animal*

✓ *After approval of a project proposal which states:*
- *Which experiments will be done and how*
- *How many animals are required*
- *The discomfort for every animal used*

✓ *After 1 year progress is evaluated.*

✓*You don't "just" do animal experiments.*

Important! The 3 R's

For every animal we use we have to consider:

✓*Replacement (Can we use a different model?) → e.g. iPSCs*

✓*Reduction (How can we use as few animals as possible?) → Inbred strains*

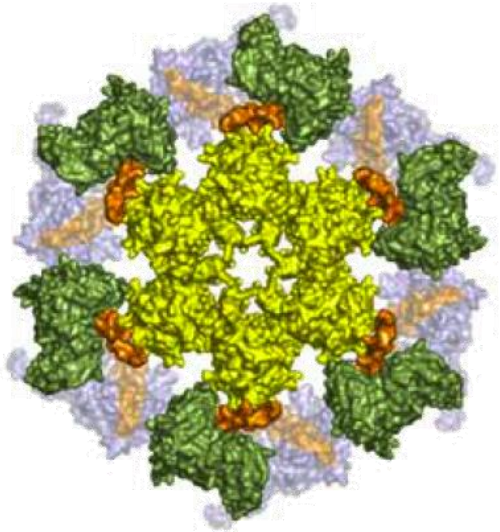
✓*Refinement (Can we reduce the discomfort the animal experiences?)*

What do we do with the mice?

Erasmus MC
University Medical Center Rotterdam

Using mouse models to study neurodevelopmental disorders

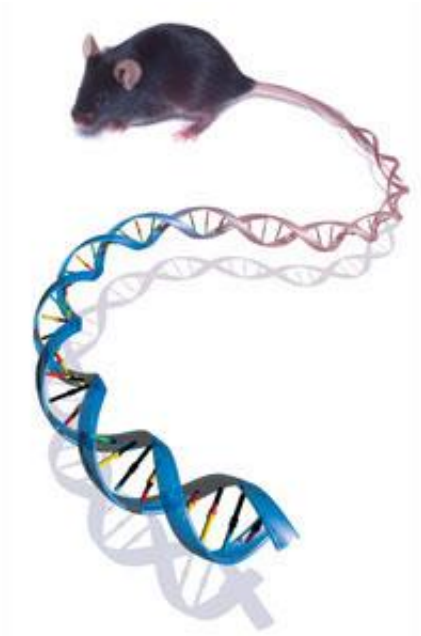
From mice to men: How fundamental science proves to be critical to understand the brain and brain disorders



SCIENCE • VOL. 257 • 10 JULY 1992

Deficient Hippocampal Long-Term Potentiation in α-Calcium-Calmodulin Kinase II Mutant Mice

Alcino J. Silva, Charles F. Stevens, Susumu Tonegawa, Yanyan Wang



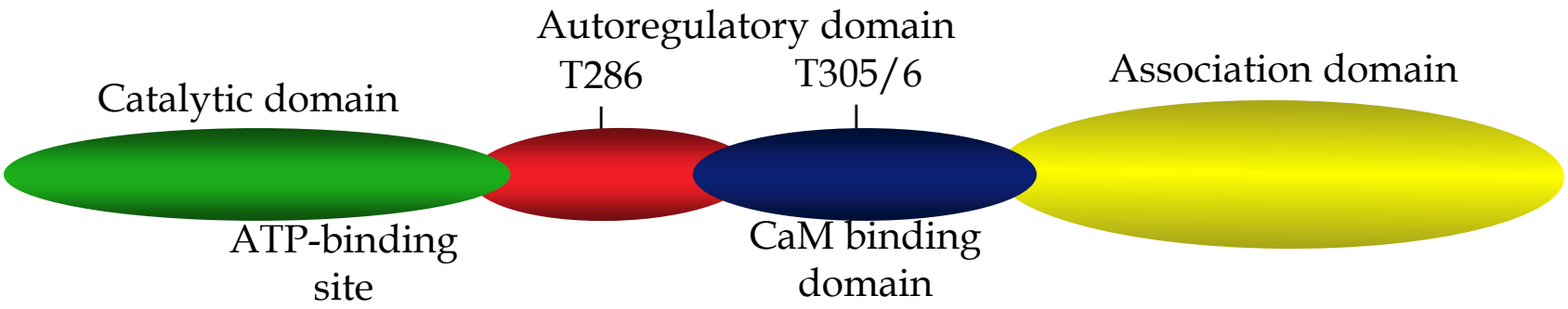
SCIENCE • VOL. 257 • 10 JULY 1992

Impaired Spatial Learning in α-Calcium-Calmodulin Kinase II Mutant Mice

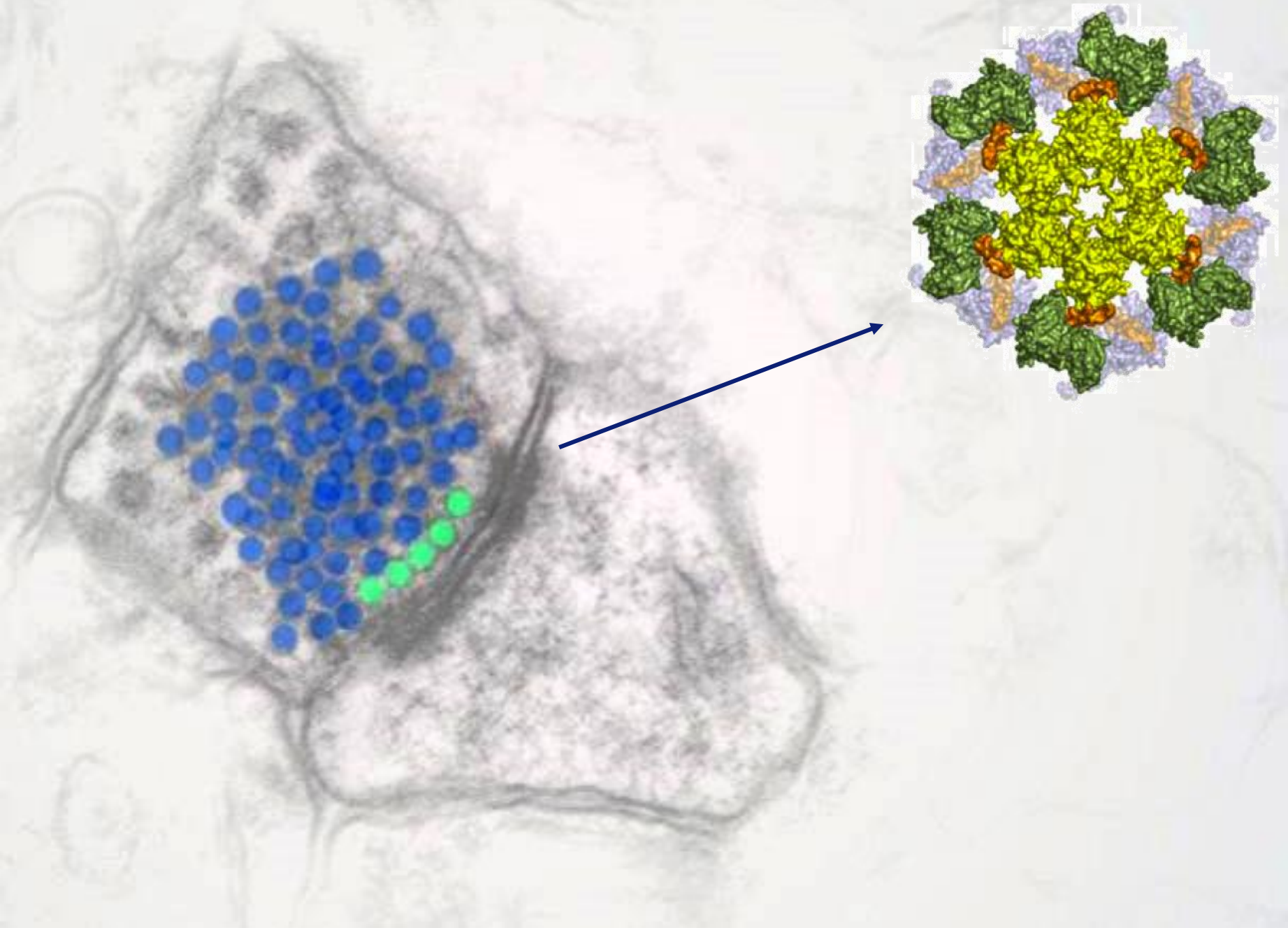
Alcino J. Silva, Richard Paylor, Jeanne M. Wehner, Susumu Tonegawa

The CAMK2 family

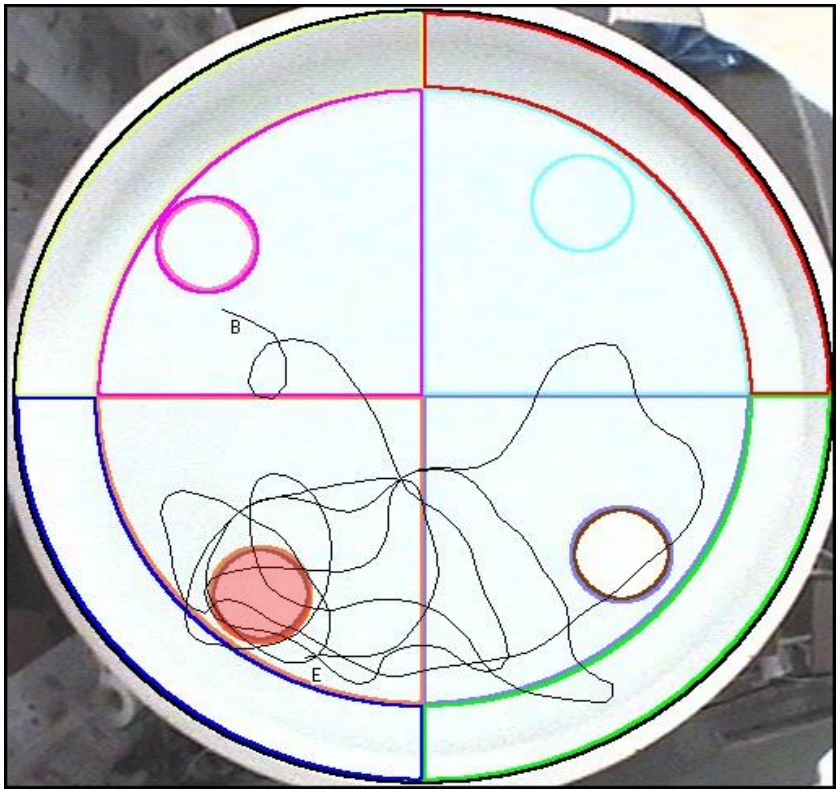
- 4 different genes encoding for 4 different proteins:
  - CAMK2A
  - CAMK2B
  - CAMK2D
  - CAMK2G
- CAMK2A and CAMK2B most abundant in the brain
- High homology between the different CAMK2s



CAMK2 plays an essential role in the Synapse



The intelligence test: Morris watermaze

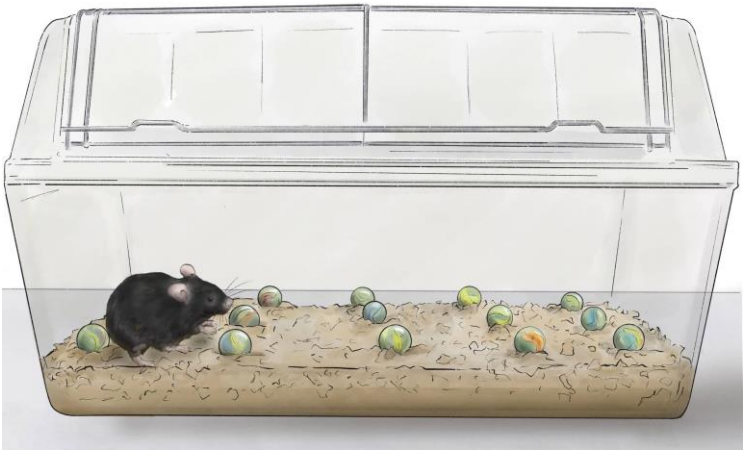


Studying motor skills (basic and advanced)

Summary CAMK2 research

- Learning and memory deficits
- Impaired motor function
- Epilepsy
- Autism Spectrum Disorder phenotypes

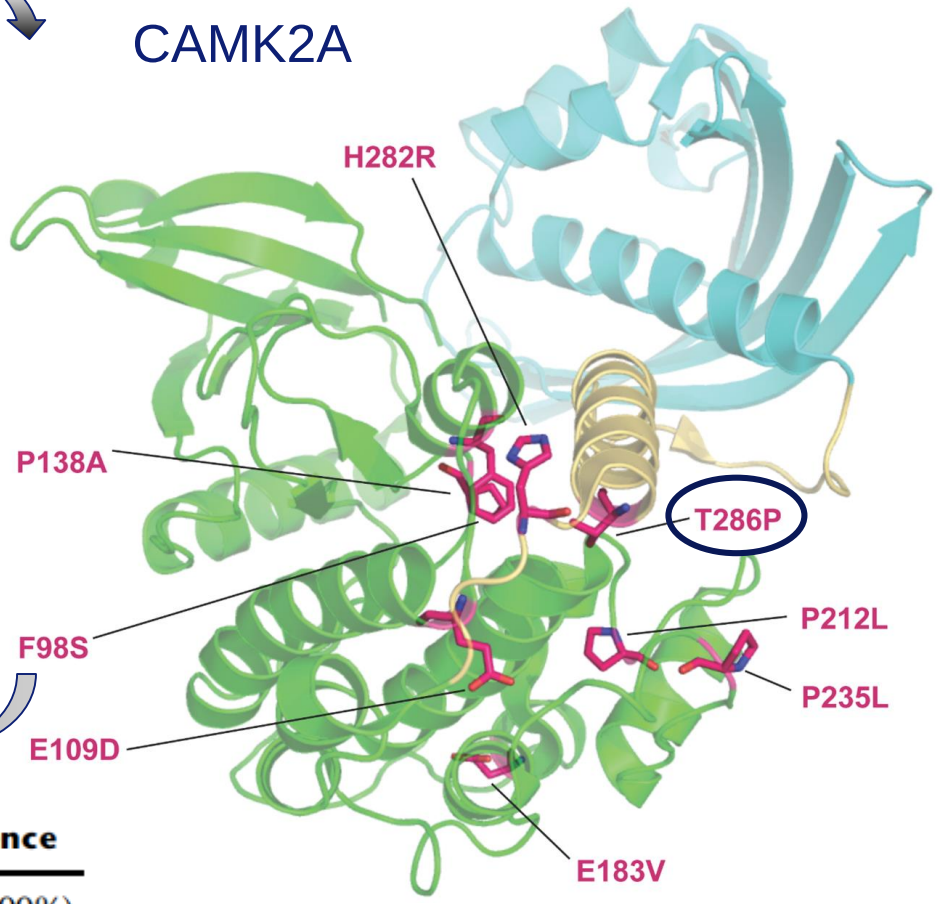
Social interaction



Marble Burying

CAMK2: from mice to men… (25 years later)

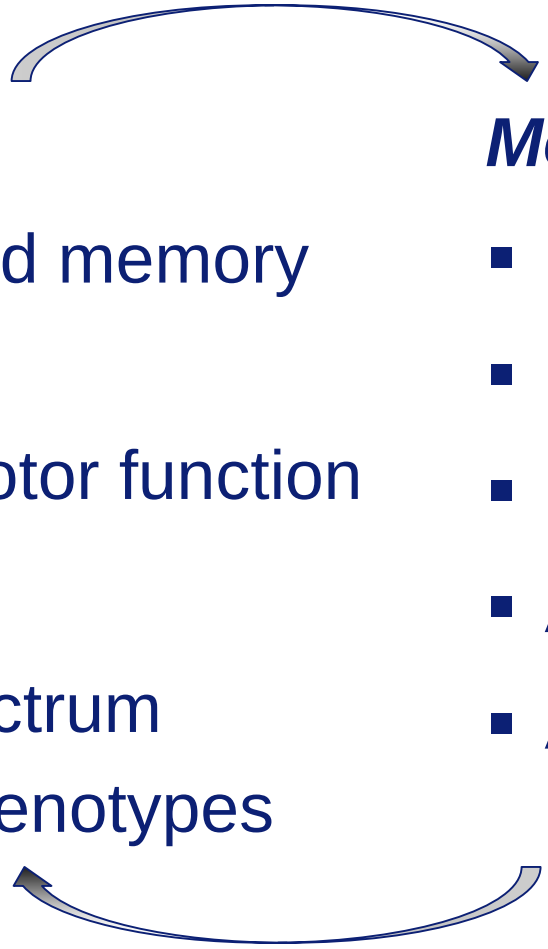
CAMK2A



Clinical Feature	Occurrence
Intellectual disability (HP:0001249)	24/24 (100%)
Delayed speech and language development (HP:0000750)	23/24 (95.8%)
Delayed gross motor development (HP:0002194)	19/24 (79.2%)

Kury, van Woerden et al., 2017, AJHG

Mice versus men



Mouse

- Learning and memory deficits
- Impaired motor function
- Epilepsy
- Autism Spectrum Disorder phenotypes

Men

- Intellectual disability
- Impaired motor function
- Epilepsy
- ASD features
- Absence of speech

What's next? Nature versus Nurture

- Family history of mental illness is the most well known risk factor for developing mental illness
- 50% of children with a mentally ill parent develop a mental disorder during their life course.
- Twin studies suggest that the development of these mental disorders is a complex interaction between nature and nurture.

- How can we test this and the underlying mechanisms in mice? What happens in the brain?

Nature versus nurture in mice

Mutant (mental ill) mom

X

Healthy dad

Healthy and mutant pups (50-50%)

Raised by mutant (mental ill) mom

Healthy mom

X

Mutant (mental ill) dad

Healthy and mutant pups (50-50%)

Raised by healthy mom

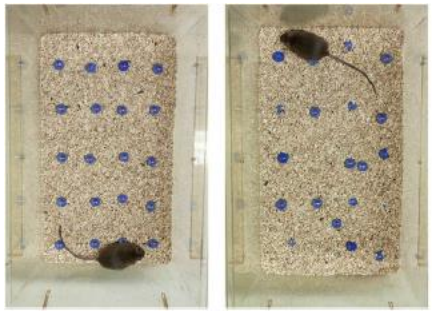
Raised by mutant (mental ill) mom

Raised by healthy mom

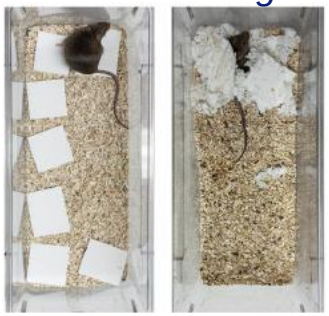
Rotarod

Open Field

Marble burying



Nest building



Forced swim

Social interaction

Morris Water Maze

Raised by mutant (mental ill) mom

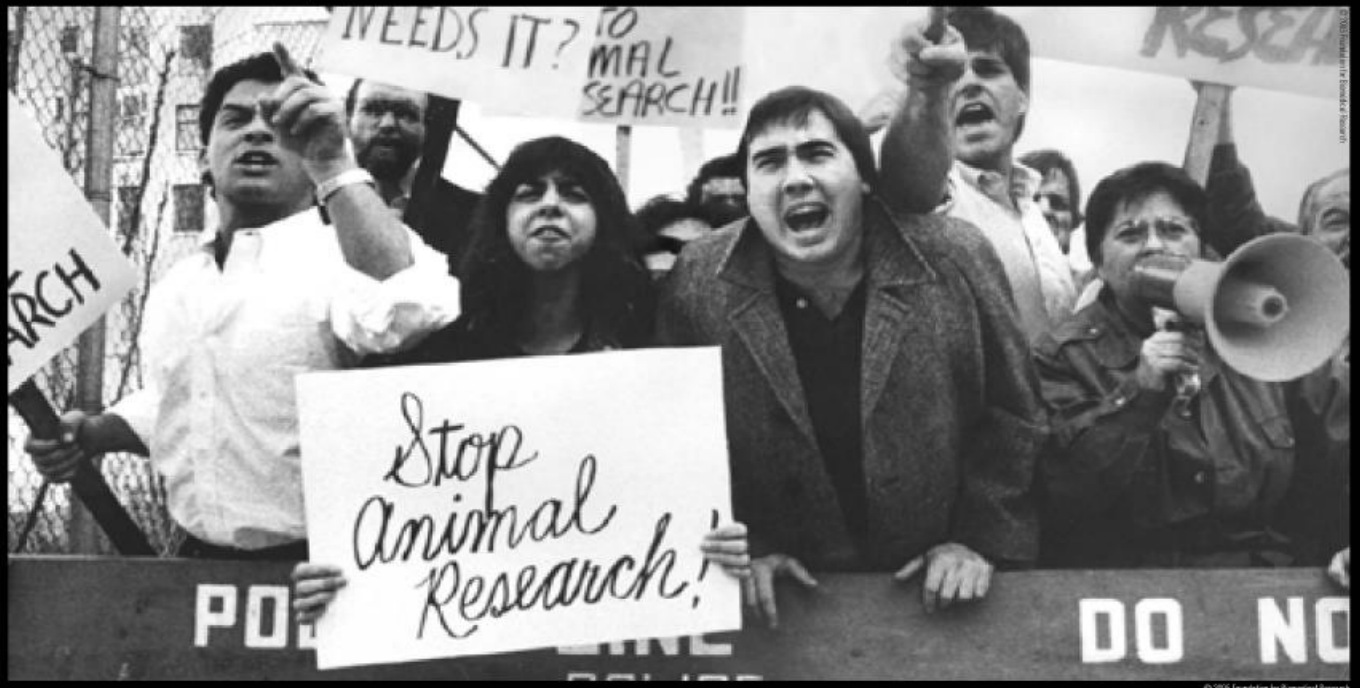
Raised by healthy mom

Brain imaging on mice

Conclusion

- Much brain research can be done in humans or in a dish
- However, if we want to know underlying mechanisms for disorders, how genes affect behavior, we still need animals
- Animals are still a requirement by law for drug testing before clinical trials
- Mice give us the perfect opportunity to study the influence of nature versus nurture (much better controlled than in humans…)

Thanks to animal research, they'll be able to protest 23.5 years longer.



According to the U.S. Department of Health and Human Services, animal research has helped extend our life expectancy by 23.5 years. Of course, how you choose to spend those extra years is up to you.

Foundation for Biomedical Research

www.fbresearch.org